19/Appeal Brief(3) 1-26-01

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Date: 12/20/00 By: Judy Mo 12-20-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

Woodle, *et al.*

SERIAL NO.: 09/139,058

FILED: August 24, 1998

FOR: **METHOD OF TREATMENT OF INFECTED TISSUES**

EXAMINER: G. Kishore

ART UNIT: 1615

Ref 1-26-01

APPEALLANT'S BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an appeal to the Board of Appeals and Interferences from the decision of Examiner Kishore mailed June 21, 2000 in which pending claims 8, 9, and 11-19 stand in final rejection.

The present paper is Appellants' Appeal Brief submitted in compliance with 37 C.F.R. §1.192.

REAL PARTY IN INTEREST

The real party in interest is Alza Corporation.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of other appeals or interferences which would directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF THE CLAIMS

Claims 8, 9, and 11-19 are pending and are the subject of this appeal. These claims are presented in Appendix A.

STATUS OF AMENDMENTS

No amendment was filed subsequent to the final rejection.

SUMMARY OF INVENTION

The invention relates to a liposome composition for treating a systemic infection that is localized at a site other than the fixed macrophages residing in the liver or the spleen (page 6, lines 19-22). Liposomes are often used as drug carriers for intravenous delivery of a therapeutic compound. However, liposomes are rapidly cleared by the cells of the reticuloendothelial system (RES) (page 5, lines 3-8). The RES can remove 80-95% of an intravenous dose of liposomes within one hour (page 5, lines 9-10), effectively limiting therapy by liposome carriers to infections within the RES (page 5, lines 12-14). The primary organs of the RES are the liver and spleen, and the fixed macrophages in these organs account for nearly 100% of the initial uptake of liposomes by the RES (page 19, lines 27-32).

The present invention provides a therapeutic liposomal composition for treatment of an infection located at a site other than the fixed macrophages in the liver and spleen. The liposomes contain vesicle forming lipids (page 18, lines 33-35) which, include a polymer-derivatized vesicle-forming lipid providing the liposomes with an extended blood circulation lifetime (page 20, lines 3-5). Entrapped in the liposomes is a therapeutic agent having activity against a pathogen causing an infection (page 7, lines 1-3). The liposomes are sized from about 0.07 to about 0.20 μm in diameter (page 23, lines 11-19). By virtue of the long blood circulation lifetime and size, the liposomes are able evade the RES and to accumulate in the infected tissue following intravenous administration (see, for example, Fig. 15A, page 35, lines 14-20; Fig. 18B, page 36, lines 26-28)).

ISSUES PRESENTED FOR REVIEW

The sole issue on appeal is whether claims 8, 9, and 11-19 are obvious under 35 U.S.C. §103 over Janoff *et al.* (U.S. Patent No. 4,897,384) or Popescu *et al.* (U.S. Patent No. 4,981,692) in

view of Yoshioka *et al.* (U.S. Patent No. 5,593,622).

GROUPING OF CLAIMS

With regard to all issues in this Appeal, claims 8, 9, and 11-19 stand or fall together.

SUMMARY OF THE REJECTIONS

1. Rejection over Janoff *et al.* in view of Yoshioka *et al.*

The Examiner characterizes Janoff *et al.* as teaching "gentamycin-containing liposomes (note the abstract, examples and claims)." The Examiner also asserts that "Janoff on columns 15-17 teaches liposomes containing PEG-cholesterol also [sic] and according to Janoff even these preparations have reduced toxicity (note col. 17)." (Office Action at pages 3-4 dated December 6, 1999).

The Examiner suggests that it is obvious, in light of Yoshioka *et al.*, to derivatize the phosphatidylinositol bisphosphate lipid ligand of Janoff *et al.* with a PEG chain in order to prevent the liposomes from aggregating, as taught by Yoshioka *et al.*

2. Rejection over Popescu *et al.* in view of Yoshioka *et al.*

The Examiner characterizes Popescu *et al.* as providing a teaching of liposomes containing an aminoglycoside antibiotic, such as gentamycin. The Examiner notes that Popescu *et al.* does teach cholesterol-PEG for use in liposomes, yet there is no teaching of phospholipids with an attached hydrophilic polymer. (Final Office action, June 21, 2000, page 2. last paragraph). However, the Examiner asserts that it would be obvious to attach PEG polymer chains to the surface of liposomes taught by Popescu *et al.* to prevent agglutination of liposomes, as taught by Yoshioka *et al.* (Final Office action, June 21, 2000, page 3, second paragraph).

APPEALLANTS' POSITION

A. Summary of Appeallants' Arguments

The claimed invention is not obvious in view of the cited references. Specifically, in the rejection over Janoff *et al.* in view of Yoshioka *et al.*, modification of the head group in the lipid ligand disclosed by Janoff *et al.* to include a polyethyleneglycol (PEG) chain, as taught by Yoshioka *et al.*, would, in fact, render the lipid ligand inoperable for its intended purpose.

Regarding the rejection over Popescu *et al.* in view of Yoshioka *et al.*, modification of the liposomes disclosed in Popescu *et al.* to include a PEG chain, as taught by Yoshioka *et al.*, would in fact inhibit uptake of the liposomes by the reticuloendothelial system (RES), thereby defeating the purpose of the liposome composition taught by Popescu *et al.*

B. THE CITED REFERENCES

JANOFF *ET AL.* relate to a composition for reducing the toxicity of therapeutic drugs. The composition consists of a complex between a drug and a ligand, where the ligand is selected according to its ability to prevent or reduce binding of the drug to the *in vivo* drug toxicity receptor (Col. 7, lines 37-42). Janoff *et al.* speculate (1) that the ligand, by forming a complex with the drug, prevents binding of the drug to the toxicity receptor *in vivo* (Col. 9, lines 53-55), and (2) that the ligand itself binds to the toxicity receptor thereby preventing drug interaction with the receptor (Col. 10, lines 2-4).

Janoff *et al.* list four embodiments of drug/lipid-ligand complexes:

(1) aminoglycoside antibiotics (*e.g.*, gentamycin) complexed with phosphatidylinositol bisphosphate (Col. 7, line 46);

(2) amphotericin B complexed with a sterol (Col. 11, line 44);

(3) adriamycin complexed with cardiolipin (Col. 12., line 50); and

(4) cisplatin complexed with phosphatidylinositol bisphosphate (Col. 12, line 64).

In each of the four embodiments, the lipid must either: (1) form a complex with the drug to prevent binding of the drug to the endogeneous receptor (Col. 9, lines 53-55); or (2) bind to the endogeneous toxicity receptor itself to prevent the drug from binding to the receptor (Col. 10, lines 2-4). Janoff *et al.* note that for cardiolipin, the head group of the lipid interacts with the toxicity receptor and the drug (Col. 12, lines 51-57). Interaction would also be expected to occur at the head group of phosphatidylinositol bisphosphate, as it is in the head group where the polar moieties are located (see structure of phosphatidylinositol bisphosphate in ATTACHMENT 1).

Janoff *et al.* do not teach or suggest liposomes that include a vesicle-forming lipid derivatized with a polymer chain, such as PEG. Moreover, modification of Janoff *et al.* in view of Yoshioka *et al.*, *i.e.*, to include derivatized lipids, would render the lipid head group unavailable for the necessary interaction with the drug and/or the toxicity receptor.

POPESCU ET AL. relate to antibiotic-containing liposomes for treatment of infections that reside in the RES, specifically in macrophages (Col. 4, lines 49-64). The liposome composition described by Popescu *et al.* is alleged to be taken up by phagocytic cells of the RES after *in vivo* administration (Col. 5, lines 2-10).

Popsecu *et al.* do not teach or suggest liposomes that include a vesicle-forming lipid derivatized with a polymer chain, such as PEG. Modification of Popescu *et al.* to include a derivatized lipid such as PEG, teaches away from the present invention as it is well know in the liposome art that liposomes containing polymer-derivatized lipid avoid uptake by the RES (see, for example, U.S. Patent No. 5,013,556). Avoiding uptake by the RES is antithical to the liposome composition of Popescu *et al.*

YOSHIOKA *ET AL.* relate to PEG-derivatized phospholipids for inhibiting adsorption of proteins on the surface of a liposome.

C. Appellants' Position

1. Regarding Janoff *et al.* in view of Yoshioka *et al.*

Janoff *et al.* relates to reducing toxicity of drugs by complexing the drug with a lipid ligand that corresponds to the drugs toxicity receptor *in vivo*. The lipid ligand in the complex must either complex with the drug, rendering the drug unavailable for interaction with the toxicity receptor *in vivo*, or the lipid ligand itself must interact with the toxicity receptor *in vivo* and thereby inhibit interaction between the drug and the toxicity receptor.

In one embodiment, the lipid ligand phosphatidylinositol bisphosphate and the drug gentamycin are described as forming a complex or a liposome. The phosphatidylinositol bisphosphate must be capable of interaction with the drug and/or with the *in vivo* toxicity receptor for the drug. To achieve either of these interactions, the head group of the phosphatidylinositol bisphosphate must be available as it is the head group of the lipid that contains the reactive/interactive moieties (see Attachment 1 and Col. 8, lines 2-6 of Janoff *et al.*).

In another embodiment, the lipid ligand cardiolipid is used in combination with the drug adriamycin (Col. 5, lines 1-68). As with the phosphatidylinositol bisphosphate, binding occurs at the head group of cardiolipin (Col. 5, lines 52-54), requiring that the head group be available for interaction.

Modification of the lipid ligand to include a polymer chain, as suggested by the Examiner, renders the lipid head group unavailable for interaction with the drug or toxicity receptor. Derivatization of a lipid with a polymer, such as polyethylene glycol (PEG), must occur at the head group of the lipid since the possible reactive moieties are localized in the head group. It is well recognized in the art that conjugation of a PEG chain to a lipid head group forms a steric "shell" about the lipid head

group. Such a shell is depicted in Figs. 3A-3B of Hristove *et al.*[1] Such a shell is known to hinder binding interaction between the lipid head group and a receptor, as described by Noppl-Simson and Needham.[2]

Therefore, modification of the lipid ligand in Janoff *et al.* to include a polymer chain, as taught by Yoshioka *et al.*, since this would likely render the lipid ligand unavailable for the necessary interaction with the drug toxicity receptor and/or the drug.

In further support of his position, the Examiner points to the disclosure of Janoff *et al.* at Cols. 15-17 of a PEG-cholesterol derivative. (Final Office action, June 21, 2000, page 3 third paragraph). The Examiner argues that the teaching of PEG-cholesterol by Janoff *et al.* renders Appellants' arguments unpersuasive, since Janoff *et al.* suggests the use of PEG-cholesterol in liposomes.

Appellants respectfully submit that the Examiner has failed to understand the teaching of Janoff *et al.* with respect to the PEG-cholesterol derivative. As set forth on Col. 11, line 46-Col. 12, line 6, in this embodiment, PEG acts to solubilize the cholesterol to provide a clear solution for injection (Col. 11, lines 57-59). Contrary to the Examiner's assertion that Janoff *et al.* teach PEG-cholesterol liposomes, <u>liposomes are explicitly excluded for use in this embodiment</u> (Col. 11, line 65 to Col. 12, line 6).

In summary, when the teaching of Janoff *et al.* is considered as a whole it is clear that a modification to the head group of a lipid ligand to include a PEG chain would render the lipid ligand inoperable for its intended purpose. Accordingly, the cited references of Janoff *et* al. and Yoshioka *et* al. cannot be properly combined and do not render Appellants' invention obvious.

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[1]Hristove and Needham, "Physical Properties of Polymer-Grafted Bilayers" in <u>STEALTH LIPOSOMES</u>, CRC Press, (1995) Chapter 5, pages 35-49; previously submitted.

[2]Noppl-Simson and Needham, *Biophys. J.*, <u>70</u>(3):1391 (1996); previously submitted.

2. Regarding Popescu *et al.* in view of Yoshioka *et al.*

Popescu *et al.* relates to a liposomal composition for treating infections which reside in the RES, specifically in macrophages (Col. 4, lines 49-64). As such, the composition described by Popescu *et al.* is intended to be, after *in vivo* administration, taken up by phagocytic cells of the RES (Col. 5, lines 2-10).

In contrast, the liposomes of the present invention are intended to avoid uptake by the RES, in order to concentrate the liposomes at a site of tissue infection. A modification of the liposomes in Popescu *et al.* to include PEG-derivatized phospholipids of Yoshioka *et al.* would prevent the liposomes from being taken up by the RES, thereby defeating the intended purpose of the composition in Popescu *et al.*

To further support his position, the Examiner notes that Popescu *et al.* teach treatment of infection caused by *Listeria ssp.* (Col. 5, line 11) and that Appellants' also disclose treatment of infection caused by *Listeria ssp.* with the claimed liposome composition (page 42, line 30 of specification). The Examiner argues that "since the bacteria are the same the sites of infection are the same." (Office action dated December 6, 1999, page 4, second paragraph).

Presumably, the Examiner is asserting that because Popescu *et al.* teach treatment of infections caused by *Listeria ssp.*, the teaching is not limited to intracellular infections of the RES. Popescu *et al.* disclose treatment of both intracellular and extracellular infections, as well as tumors, cysts, allergies, etc. (Col. 4, lines 41-43). Yet, as described on Col. 5, lines 45-59, treatment of extracellular infections (*i.e.*, infections outside the RES) is achieved by uptake of the liposomes into the macrophages of the RES. The macrophages then carry the active agent within the liposomes to the site of infection. Thus, even for treatment of extracellular infections the teaching of Popescu *et al.* is limited to uptake of the liposomal composition by the RES.

A reference must be considered for all it teaches. Popescu *et al.* is concerned with treatment of infections by RES macrophage uptake of drug-laden liposomes. Modification of the liposomes of Popescu *et al.* to include hydrophilic polymer chains, in accord with the teaching of Yoshioka *et al.*, would inhibit uptake of the liposomes by the RES, thereby rending liposome composition unable to fulfill its intended purpose.

CONCLUSIONS

In view of the foregoing remarks, Appellants submit that the pending claims are in condition for allowance and patentably define over the prior art, and urge the Board to overturn the Examiner's rejections.

Respectfully submitted,

Judy M

Date: 12/20/00

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APPENDIX A: CLAIMS ON APPEAL

8. For use in a method of treating a site of systemic infection which is localized at a tissue site other than the fixed macrophages residing in the liver or the spleen, an injectable liposome composition which:

(a) is comprised of a vesicle-forming lipid and between about 1-20 mole percent of an amphipathic vesicle-forming lipid derivatized with a hydrophilic biocompatible polymer selected from the group consisting of polyglycolic acid (PGA), polylactic acid (PLA), a copolymer of PGA and PLA, polyvinyl alcohol and polyethyleneglycol, said polymer being of a size and in a molar amount effective to extend liposome blood circulation time, measured 24 hours after said injection, over that achievable in the absence of the hydrophilic polymer,

(b) is composed of liposomes having a selected mean particle diameter in the size range between about 0.07-0.20 microns;

(c) contains in liposome-entrapped form, a therapeutic compound active against the pathogen causing the infection, and

(d) is able to accumulate selectively in the infected tissue following intravenous administration, thereby to concentrate liposome-entrapped drug at the infection site.

9. The composition of claim 8, wherein the hydrophilic polymer is a polyethyleneglycol having a molecular weight between about 300-5,000 daltons.

11. The composition of claim 8, for use in treating such an infected region wherein the therapeutic compound is an aminoglycoside antibiotic, and the concentration of compound entrapped in the liposomes is greater than about 20 μg compound/μmole liposome lipid.

12. The composition of claim 8, wherein the site of infection is the lung, and the aminoglycoside antibiotic is gentamicin.

13. A method of preparing a therapeutic agent for localization in an infected region of tissue, when the agent is administered by intravenous injection, comprising

entrapping the agent in liposomes which:

(a) are comprised of a vesicle-forming lipid and between about 1-20 mole percent of an amphipathic vesicle-forming lipid derivatized with a hydrophilic biocompatible polymer selected from the group consisting of polyglycolic acid (PGA), polylactic acid (PLA), a copolymer of PGA and PLA, polyvinyl alcohol and polyethyleneglycol, said polymer being of a size and in a molar amount effective to extend liposome blood circulation time, measured 24 hours after said injection, over that achievable in the absence of the hydrophilic polymer,

(b) have a selected mean particle diameter in the size range between about 0.07-0.20 microns;

(c) contain in liposome-entrapped form, a therapeutic compound effective against the source of the infection; and

(d) are able to accumulate selectively in the infected tissue following intravenous administration, thereby to concentrate liposome-entrapped drug at the infection site.

14. The method of claim 13, wherein the agent is an aminoglycoside antibiotic drug.

15. The method of claim 14, wherein the aminoglycoside is gentamicin.

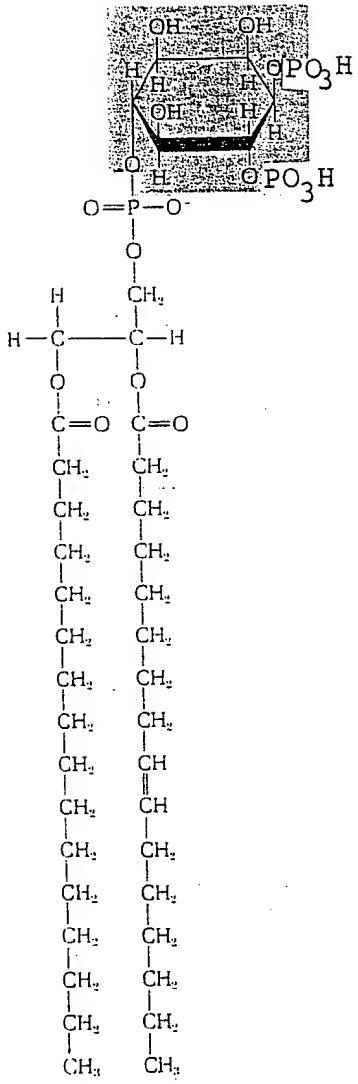
16. The composition of claim 8, wherein the therapeutic compound is an agent selected from the group consisting of antibacterial agents, antiviral agents and antifungal agents.

17. The composition of claim 16, wherein the antibacterial agent is a quinolone antibiotic.

18. The method of claim 13, wherein the therapeutic compound is an agent selected from the group consisting of antibacterial

agents, antiviral agents and antifungal agents.

19. The method of claim 18, wherein the antibacterial agent is a quinolone antibiotic.



Phosphatidylinositolbisphosphate

Attorney Docket No. 5325-0122.20

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Date: 12/20/00 By: Judy Mohr

PATENT

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EXAMINER: G. Kishore

ART UNIT: 1615

Appeal Brief Transmittal

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal submitted September 21, 2000, enclosed herewith are the following:

☒ Applicant's Appeal Brief in triplicate

☒ Petition for 1-Month Extension of Time

☒ Fees (37 CFR 1.17(c)): ☒ Large Entity: $310.00

☒ A check for $420.00 ($310.00 + $110.00) covering the above fee is enclosed.

☒ Please charge any underpayment for timely consideration of this paper to Deposit Account No. 04-0531.

☒ Applicant petitions for an Extension of Time if necessary for timely filing of this Brief.

Respectfully submitted,

Judy Mohr

Date: 12/20/00

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